(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 March 2004 (25.03.2004)

PCT

(10) International Publication Number
WO 2004/024147 A1

(51) International Patent Classification[7]: A61K 31/415, A61P 31/18, C07D 231/18, C07C 255/54

(21) International Application Number: PCT/IB2003/003946

(22) International Filing Date: 8 September 2003 (08.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0221477.3 16 September 2002 (16.09.2002) GB
0223354.2 8 October 2002 (08.10.2002) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

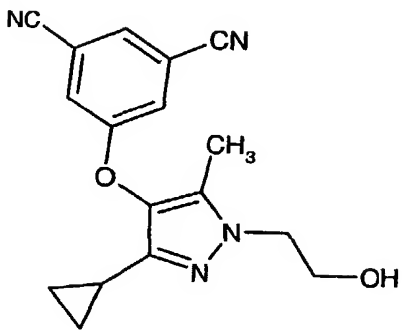
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/024147 A1

(54) Title: 4-(3,5-DICYANOPHENOXY) PYRAZOLE DERIVATIVES FOR USE AS TRANSCRIPTASE MODULATORS IN THE TREATMENT OF I.A. HIV



(I)

(57) Abstract: This invention relates to the pyrazole derivatives of formula (I) and pharmaceutically acceptable salt, solvate or derivatives thereof, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes. The compounds of the invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors, thereof. Reverse transcriptase is implicated in the infectious lifecycle of Human Immunodeficiency Virus (HIV). Compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions caused by HIV and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

4-(3,5-DICYANOPHENOXY)PYRAZOLE DERIVATIVES FOR USE AS REVERSE TRANSCRIPTASE MODULATORS IN THE TREATMENT OF I.A. HIV

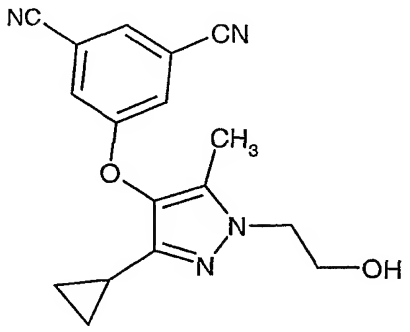
This invention relates to pyrazole derivatives, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes.

Reverse transcriptase is implicated in the infectious lifecycle of Human Immunodeficiency Virus (HIV). Compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions caused by HIV and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS). There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase, since the virus is able to mutate, becoming resistant to the effects of known modulators.

A class of N-phenylpyrazoles which act as reverse transcriptase inhibitors are disclosed in *J. Med. Chem.*, 2000, **43**, 1034. Antiviral activity is ascribed to a class of N-(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200. International Application No. PCT/IB02/01234, unpublished at the filing date of the instant application, generically embraces, but does not specifically disclose, the compound of formula (I) below.

The compounds of the invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors, thereof.

According to the invention there is thus provided the compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof.

The pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, chloride, bromide, iodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, fumarate, pamoate, aspartate, besylate, carbonate, bicarbonate/, camsylate, D and L-lactate, D and L-tartrate, esylate, mesylate, malonate, orotate, gluceptate, methylsulphate, stearate, glucuronate, 2-napsylate, tosylate, hibenzate, nicotinate, isethionate, malate, maleate, citrate, gluconate, succinate, saccharate, benzoate, esylate, and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc, choline, diolamine, olamine, arginine, glycine, tromethamine, benzathine, lysine, meglumine and diethylamine salts.

For reviews on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977 and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York, 1996, Vol 13, pp453-497

The pharmaceutically acceptable solvates of the compounds of formula (I) include the hydrates thereof.

The compound of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compound. Examples of such derivatives are described in: Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538; Topics in Chemistry, Chapter 31, pp 306 – 316; and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference) and include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, sulphonamides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

The invention encompasses all isomers of the compound of formula (I) and pharmaceutically acceptable salts, solvates or derivatives thereof, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or high performance liquid

chromatography (HPLC) of a stereoisomeric mixture of compounds. An individual enantiomer of a compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support, or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

The compound of formula (I) and pharmaceutically acceptable salts, solvates or derivatives thereof may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such polymorphic forms ("polymorphs") are encompassed within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both, and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behaviour, and melting point of the compound are used to distinguish polymorphs.

The compound of formula (I), pharmaceutically acceptable salts, solvates and derivatives thereof, isomers thereof, and polymorphs thereof, are hereinafter referred to as the compounds of the invention.

Preferred compounds of the invention are the compound of formula (I) and its pharmaceutically acceptable salts and solvates thereof.

The most preferred compound of the invention is the compound of formula (I).

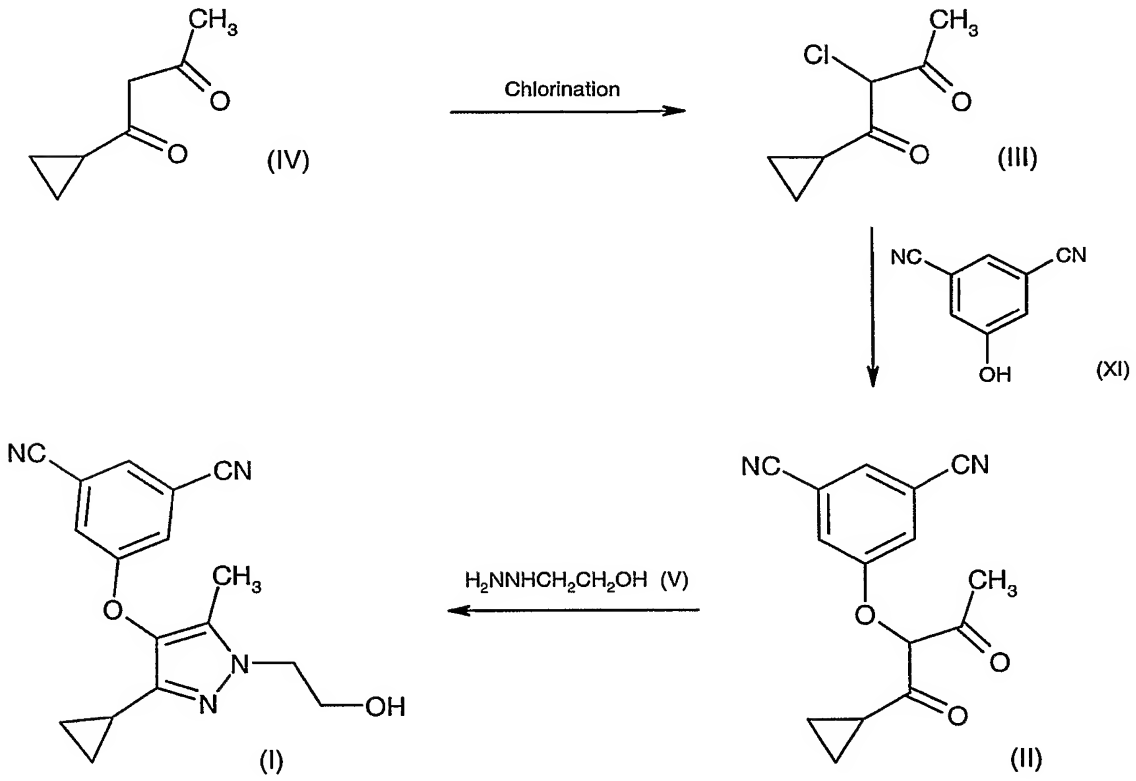
The compounds of the invention exhibit advantageous properties, including excellent metabolic stability, leading to excellent pharmacokinetic properties. In addition, the compounds of the invention may have advantages over those of the prior art with regard to a number of other useful properties, such as potency, duration of action, spectrum of activity, side effect profile, solubility, chemical stability, and so on.

The compounds of the invention may be prepared by any method known in the art for the preparation of compounds of analogous structure. The compounds of the invention can be prepared by the procedures described in the methods below, or by the specific methods described in the Examples, or by similar methods to either. The invention also encompasses any one or more of these

processes for preparing the compounds of the invention, in addition to any novel intermediates used therein.

The compound of formula (I) may be prepared according to the route shown in Scheme 1 below.

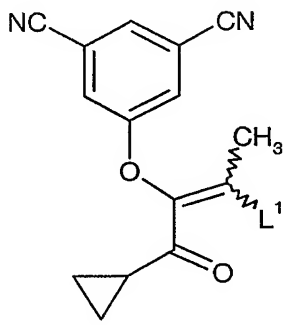
Scheme 1



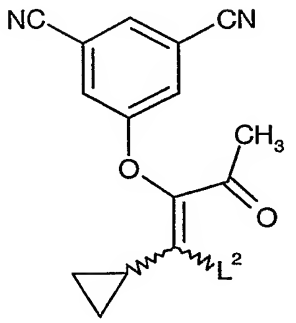
In Scheme 1, the compound of formula (I) may be prepared by condensation of the compound of formula (II) with 2-hydroxyethylhydrazine of formula (V) or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of formula (II) in a suitable solvent, such as acetic acid, is treated with the hydrazine of formula (V), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction is carried out at room temperature.

Functional equivalents of the compound of formula (II) may also be used in this reaction. These include compounds of formulae (VI) or (VII), in which L^1 and L^2,

respectively, are each suitable leaving groups, preferably -N(C_1-C_6 alkyl)$_2$, most preferably -N(CH_3)$_2$.



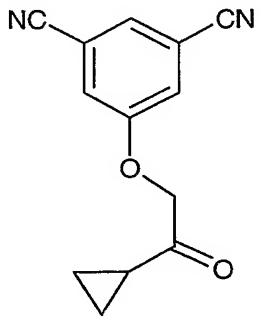
(VI)



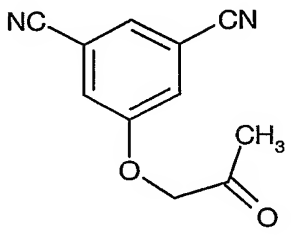
(VII)

Thus, the compound of formula (I) may be prepared by condensation of a compound of formulae (VI) or (VII) with the compound of formula (V), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of formula (VI) or (VII) in a suitable solvent, such as ethanol, is treated with the compound of formula (V), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Compounds of formula (VI) in which L^1 is dimethylamino may be prepared by the reaction of the compound of formula (VIII) with an appropriately substituted formamide acetal at an elevated temperature, preferably at about 100°C. Compounds of formula (VII) in which L^1 is dimethylamino may be prepared by the reaction of the compound of formula (IX) under the same conditions.

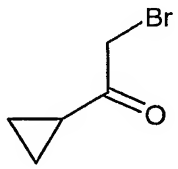


(VIII)



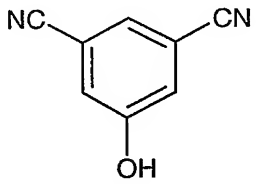
(IX)

The compound of formula (VIII) is either commercially available or may be prepared by the reaction of the compound of formula (X)



(X)

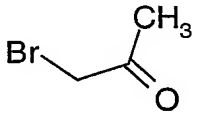
with the compound of formula (XI)



(XI)

In a typical procedure, a solution of the compound of formula (XI) in a suitable solvent, such as acetone, is treated with a suitable base, such as caesium carbonate, and the compound of formula (X). In a preferred procedure, the reaction mixture is heated, for example under reflux. Optionally, a nucleophilic catalyst such as sodium iodide or tetrabutylammonium iodide may be added.

The compound of formula (IX) is either commercially available or may be prepared from the compound of formula (XII)



(XII)

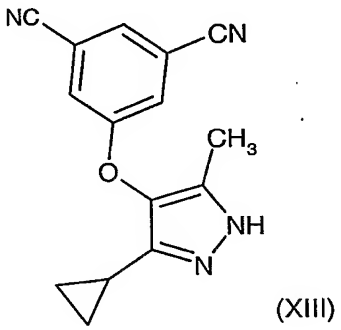
and the compound of formula (XI) in the same way that the compound of formula (VIII) may be prepared from the compound of formula (X).

The compound of formula (II) may be prepared by the reaction of the compound of formula (III) with the compound of formula (XI).

In a typical procedure, a solution of the compound of formula (III) in a suitable solvent such as acetone is treated with the compound of formula (XI) and a suitable base, such as potassium or caesium carbonate, and heated, preferably under reflux. Optionally, a nucleophilic catalyst such as sodium iodide or tetrabutylammonium iodide may be added.

The compound of formula (III) is either commercially available or may be prepared by reaction of the compound of formula (IV) with a chlorinating reagent. In a typical procedure, a cooled solution of the compound of formula (IV) in a suitable solvent such as acetonitrile is treated first with tetrabutylammonium bromide and chlorotrimethylsilane and then dry dimethylsulphoxide. In another typical procedure, the compound of formula (IV) is treated with sulphuryl chloride, optionally in the presence of a suitable solvent such as dichloromethane.

The compound of formula (I) may also be prepared by reaction of the pyrazole of formula (XIII)



(XIII)

with an alkylating agent of formula (XIV)

$$Lg\text{-}CH_2CH_2OH \quad (XIV)$$

or a protected derivative thereof.

In a typical procedure, a solution of the pyrazole of formula (XIII) in a suitable solvent such as ethanol or N,N-dimethylformamide is treated with an alkylating agent of formula (XIV) such as a protected hydroxyethyl bromide and a base such as sodium ethoxide or sodium hydride and heated at a temperature of from 0°C to the reflux temperature of the solvent. A preferred combination is N,N-dimethylformamide as the solvent, sodium hydride as the base, 0°C as the temperature and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran as the alkylating agent.

As will be appreciated by the skilled artisan, in the alkylation of the pyrazole of formula (XIII) it may be necessary or desirable to protect the OH group of the compound of formula (XIV), in which case the compound of formula (I) is finally prepared by deprotection of the corresponding compound bearing an $-OP^1$ group, wherein P^1 is a suitable protecting group. Examples of suitable protecting groups

will be apparent to the skilled person; see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons (in particular pages 10 - 118, relating to protection for the hydroxyl group), incorporated herein by reference. Such compounds bearing an $-OP^1$ group may be prepared using the routes described above, *mutatis mutandis.*

Compounds of formulae (IV) and (V) are either commercially available, known from the literature or easily prepared by methods well known to those skilled in the art.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the invention can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the invention may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the compounds of the invention may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

A formulation of the tablet could typically contain from 0.01mg to 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

Ingredient	%w/w
Compound of the invention	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose sodium	3.000
Magnesium Stearate	1.500

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 5 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the invention may contain from 1 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will appreciate that, in the treatment of certain conditions the compounds of the invention may be taken as a single dose as needed or desired.

The compounds of invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Oral administration is preferred.

Included within the scope of the invention are embodiments comprising the co-administration of a compound of the invention with one or more additional therapeutic agents, and compositions containing a compound of the invention along with one or more additional therapeutic agents. Such a combination therapy is especially useful for the prevention and/or treatment of infection by HIV and related retroviruses which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the invention. For example, in the treatment of an HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections, neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the invention include simultaneous or sequential treatment with a compound of the invention and one or more:

(a) reverse transcriptase inhibitors such as abacavir, adefovir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine;

(b) non-nucleoside reverse transcriptase inhibitors such as capavirine, delavirdine, efavirenz, and nevirapine;

(c) HIV protease inhibitors such as indinivir, nelfinavir, ritonavir, and saquinavir;

(d) CCR5 antagonists such as TAK-779 or UK-427,857;

(e) CXCR4 antagonists such as AMD-3100;

(f) integrase inhibitors, such as L-870,810 or S-1360;

(g) inhibitors of viral fusion such as T-20;

(h) investigational drugs such as trizivir, KNI-272, amprenavir, GW-33908, FTC, PMPA, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 or TMC-125;

(i) antifungal agents, such as fluconazole, itraconazole or voriconazole; or

(j) antibacterial agents, such as azithromycin.

The activity of the compounds of the invention as reverse transcriptase inhibitors may be measured using the following assay.

Inhibition of HIV-1 reverse transcriptase enzyme

Using purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli, a 96-well plate assay system is established for assaying a large number of samples using either the Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) or the [3H]-flashplate enzyme assay system (NEN - SMP 103) and following the manufacturer's recommendations. The compounds are dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity is expressed in percent inhibition relative to DMSO control. The concentration at which compound inhibits reverse transcriptase by 50% is expressed as the IC_{50} of the compound.

The compound of Example 1, when tested according to the above procedure, had an IC_{50} value of 295 nanomolar.

The metabolism of the compounds of the invention may be measured using the following assays.

A. Metabolism in human liver microsomes and Supermix™

The metabolic vulnerability of the compounds of the invention in microsomes and Supermix ™ may be assayed as follows.

The microsomal fraction is isolated from several human livers and the P450 content determined. Supermix™ is obtained from Gentest. Human microsomes (0.5μM cytochrome P450) and Supermix™ (0.05μM cytochrome P450) are added to an incubation media containing 50mM phosphate buffer (pH7.4), 5mM $MgCl_2$, 1mM NADP and an NADPH generating system consisting of isocitrate and isocitrate dehydrogenase. The substrate concentration is 1μM and incubations are carried out at 37°C for 1 hour. Samples are taken at time points throughout this period and analysed using hplc-ms-ms assay.

The compound of Example 1, when tested according to the above procedure, had a t ½ value of >120 minutes (both human microsomal and Supermix ™).

B. Metabolism in Human hepatocytes.

The metabolic vulnerability of the compounds of the invention in human hepatocytes may be assayed as follows.

Cryopreserved human hepatocytes are obtained from *In vitro* Technologies, Inc. The hepatocytes are thawed and suspended at 1 million cells/ml in 50% Krebs-Heinsleit buffer : 50% Williams E media containing 10% foetal bovine serum. The substrate concentration is 3μM and incubations are carried out at 37°C for 3 hours. Samples are taken at time points throughout this period and analysed using hplc-ms-ms assay.

The compound of Example 1, when tested according to the above procedure, had an unbound hepatocyte clearance value of <9 ml/min/kg.

Thus the invention provides:

(i) the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;

(ii) a process for the preparation of the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;

(iii) a pharmaceutical composition including the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) the compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a reverse transcriptase inhibitor or modulator;

(vi) the compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS);

(vii) the use of the compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity;

(viii) the use of the compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS);

(ix) a method of treating an HIV or a genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS), comprising administering an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof; and

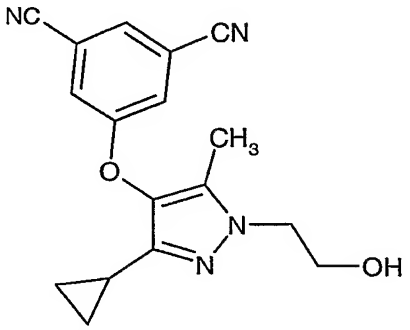
(xi) certain novel intermediates disclosed herein.

The following Examples illustrate the preparation of the compounds of formula (I). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million (ppm) downfield from tetramethylsilane using conventional abbreviations for designation of major peaks, e.g.: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: HRMS, high resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F_{254} plates, R_f being the distance travelled by a compound divided by the distance travelled by the solvent front on the TLC plate.

EXAMPLE 1

5-{[3-Cyclopropyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile



2-Hydroxyethylhydrazine (1.15ml, 16.9mmol) was added to a solution of the diketone from Preparation 7 (4.1g, 15.4mmol) in acetic acid (40ml) under nitrogen at room temperature. After stirring for 18 hours, the mixture was concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane (50:50 changing to 100:0, by volume) to provide samples of the two regioisomers which required further purification.

The less polar fraction was isolated as a yellow solid (1.2g), a sample of which (815mg) was purified by recrystallisation from toluene (5ml) to give the title compound as colourless needles (600mg). A sample of this material (580mg) was further purified by preparative HPLC using a Luna C8(II) 150x21.2mm 10μm column eluting with 95:5 water:acetontrile (0.1% aqueous trifluoroacetic acid) and acetonitrile (0-1min 100:0 then over 1 min changing to 70:30 for 18min then changing to 100:0 over 1min) to provide a sample of the title compound. This material was freed of any remaining acid by dissolving in dichloromethane (50ml) and washing with saturated aqueous sodium bicarbonate solution (50ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide a foam (270mg) which was recrystallised from toluene (5ml) to give a sample of the title compound as colourless needles (265mg). M.p. 127-128 °C.

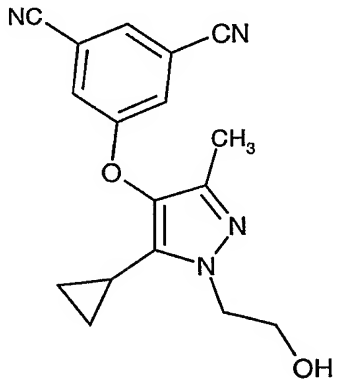
^{1}H NMR (400MHz, $CDCl_3$): δ = 0.84 (m, 4H), 1.58 (m, 1H), 2.13 (s, 3H), 4.03 (m, 2H), 4.13 (m, 2H), 7.42 (s, 2H), 7.59 (s, 1H).

LRMS (atmospheric pressure chemical ionisation) : m/z [MH^+] 309.

Microanalysis: Found C, 66.14; H, 5.24; N, 18.15. $C_{17}H_{16}N_4O_2$ requires C, 66.22; H, 5.23; N, 18.17%.

Regioisomer confirmed by nOE NMR and unambiguously identified by X-ray crystallography.

The more polar fraction was further purified by flash chromatography on silica gel eluting with ethyl acetate:toluene (50:50, by volume) to give 5-{[5-cyclopropyl-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile (structure below)



as a white solid (90mg). M.p. 129-130 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.68 (m, 2H), 0.87 (m, 2H), 1.58 (m, 1H), 2.03 (s, 3H), 4.07 (m, 2H), 4.31 (m, 2H), 7.39 (s, 2H), 7.59 (s, 1H).
LRMS (atmospheric pressure chemical ionisation): m/z [MH^+] 309.

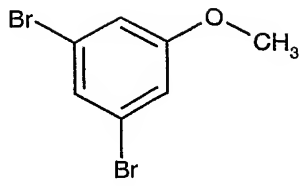
EXAMPLE 2

5-{[3-Cyclopropyl-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy}isophthalonitrile

To a stirred solution of the pyrazole from Preparation 9 (250mg, 0.64mmol) in methanol (6ml) was added *para*-toluenesulfonic acid (12mg, 0.06mmol). After 18 hours the reaction mixture was concentrated and the residue was partitioned between 10% aqueous potassium carbonate solution (20ml, w/v) and dichloromethane (20ml). The separated aqueous layer was washed with dichloromethane (2 x 20ml) and the combined organic components were dried over magnesium sulfate, filtered and concentrated to give the title compound as a pale yellow oil (195mg) which was used without further purification.
^{1}H NMR (400mHz, $CDCl_3$) consistent with that described above.
LRMS (thermospray): m/z [MH^+] 309.

PREPARATION 1

1,3-Dibromo-5-methoxybenzene

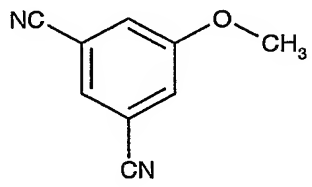


Sodium methoxide (8.80ml of a 4.5M solution in methanol, 39.6mmol) was added dropwise to a stirred solution of 3,5-dibromofluorobenzene (5.00g, 19.0mmol) (Aldrich) in *N,N*-dimethylformamide (95ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature, stirred for 1 hour and then concentrated under reduced pressure. The residue was dissolved in ether (500ml) and the resulting solution was washed with water (3x300ml) and brine (300ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (5.13g) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.79 (s, 3H), 7.00 (s, 2H), 7.26 (s, 1H).
LRMS (thermospray): m/z [MH^+] 266.
Microanalysis: Found: C, 31.56; H, 2.29. $C_7H_6OBr_2$ requires C, 31.62; H, 2.27%.

PREPARATION 2

3,5-Dicyanomethoxybenzene



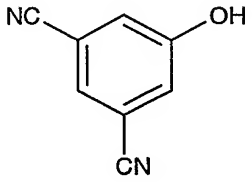
Tris(dibenzylideneacetone)dipalladium(0) (6.53g, 7.15mmol) was added in one portion to a stirred solution of the bromide of Preparation 1 (38.0g, 143mmol), 1,1'-bis(diphenylphosphino)ferrocene (9.3g, 16.8mmol) and zinc cyanide (20.0g, 172mmol) in *N,N*-dimethylformamide (300ml) at room temperature under nitrogen. The reaction was heated at 100°C for 14 hours and cooled to room temperature. Water (1500ml) was added and the mixture was extracted with ethyl acetate (3x500ml). The combined organics were filtered and the filtrate was washed with water (500ml), dried over magnesium sulphate, filtered and

concentrated under reduced pressure. The resulting solid was triturated with toluene (1000ml) to provide the title compound (18.0g) as a tan solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.83 (3H, s), 7.31 (2H, s), 7.48 (1H, s).

PREPARATION 3

3,5-Dicyanohydroxybenzene

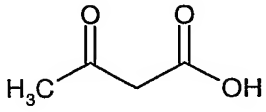


The nitrile of Preparation 2 (9.60g, 60.7mmol) was added portionwise to a stirred suspension of aluminium trichloride (32.4g, 243mmol) in dichloromethane (250ml) at 0°C under nitrogen. The suspension was heated to 45°C and stirred for 6 days. The reaction was cooled to room temperature and cautiously poured onto ice (450ml). Concentrated hydrochloric acid (450ml) was added dropwise and the resulting suspension was stirred for 10 minutes at room temperature. The resulting solid was collected by filtration, washed with water and dried over phosphorus pentoxide to provide the title compound (7.83g) as a tan solid containing approximately 11 % starting material by ^{1}H-NMR and microanalysis.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.56 (m, 1H).

PREPARATION 4

3-Oxobutanoic acid



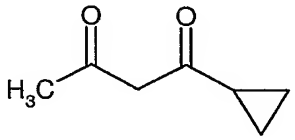
Sodium hydroxide (37.9g, 0.947mol) was dissolved in water (770ml) and was added dropwise over 20min to 3-oxo-butanoic acid methyl ester (100g, 0.861mol) (Aldrich) at room temperature with stirring. The reaction was stirred for 18 hours, quenched with ammonium sulfate (700g) and acidified slowly with a solution of concentrated hydrochloric acid (21.5ml) in water (250ml) with ice cooling. The reaction mixture was extracted with diethylether (6x200ml) and the combined organic extracts were dried over magnesium sulphate, filtered and concentrated

under reduced pressure to provide the title compound (58.2g) as a pale yellow oil which was a mixture of keto:enol tautomers (as observed in ^{1}H NMR).

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.00 (s, 3H-enol), 2.30 (s, 3H-keto), 3.51 (s, 2H-keto), 5.02 (s, 1H-enol).

PREPARATION 5

1-Cyclopropyl-1,3-butanedione



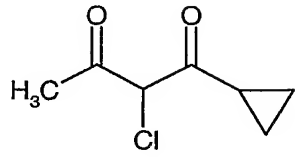
Magnesium turnings (3.04g, 125mmol) suspended in methanol (145ml) were heated to reflux under nitrogen for 1 hour, cooled to room temperature and the β-keto acid from Preparation 4 (25.5g, 250mmol) dissolved in methanol (25ml) was added dropwise with ice-cooling. The reaction was stirred for 1 hour at room temperature and the solvent was removed under reduced pressure to give the magnesium salt of the acid. Meanwhile, cyclopropane-carboxylic acid (9.91ml, 125mmol) was dissolved in dimethylformamide (200ml) and carbonyldiimidazole (22.4g, 138mmol) was added portionwise under nitrogen at 0°C. This was stirred for 1.5 hour and the magnesium salt from above was added as a solution in dimethylformamide (100ml) at 0°C. The reaction was allowed to stir at room temperature for 92 hours and the mixture was poured into 2M aqueous hydrochloric acid (85ml) then diluted with water (170ml). The mixture was extracted with diethylether (6x200ml) and the combined organic extracts were washed with brine (3x200ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual orange oil was purified by flash chromatography on silica gel eluting with pentane:diethylether (100:0 changing to 90:10 then 80:20, by volume) to provide the title compound (7.39g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.89 (m, 2H), 1.08 (m, 2H), 1.59 (m, 1H), 2.00 (s, 3H), 5.61 (s, 1H), 15.62 (s, 1H).

LRMS (electrospray) : m/z [MNa^+] 149.

PREPARATION 6

2-Chloro-1-cyclopropyl-1,3-butanedione



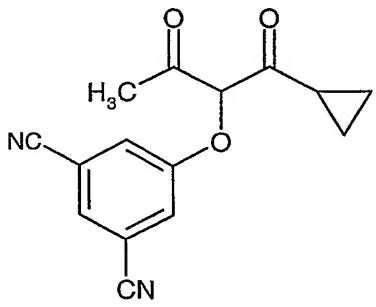
Chlorotrimethylsilane (18.9ml, 174mmol) was added to a solution of tert-butylammonium bromide (932mg, 2.89mmol) in dry acetonitrile (50ml) under nitrogen at room temperature and the mixture was cooled to 0°C. The diketone from Preparation 5 (7.3g, 57.9mmol) in acetonitrile (36ml) was then added followed by dropwise addition of dry dimethylsulfoxide (12.3ml, 174mmol). The reaction was stirred at 0°C for 1.5 hours and the mixture was diluted with water (500ml), extracted with diethylether (2x200ml and 100ml) and the combined organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel eluting with pentane:diethylether (100:0 changing to 95:5 then 90:10, by volume) to provide the title compound (5.76g) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.04 (m, 2H), 1.18 (m, 2H), 2.27 (s, 3H), 2.42 (m, 1H), 15.78 (s, 1H).

LRMS (electrospray): m/z [M-H$^+$] 159.

PREPARATION 7

5-[1-(Cyclopropylcarbonyl)-2-oxopropoxy]isophthalonitrile



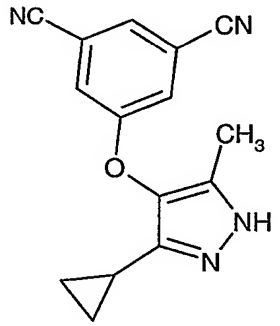
Cesium carbonate (6.01g, 18.5mmol) and the phenol from Preparation 3 (2.66g, 18.5mmol) were added to a stirred solution of the diketone from Preparation 6 (2.46g, 15.4mmol) in acetone (75ml) under nitrogen at 60°C and the reaction was stirred for 3 hours. After cooling the acetone was removed under reduced

pressure and the residue was partitioned between 1N aqueous hydrochloric acid (100ml) and dichloromethane (100ml). The aqueous phase was separated and extracted with dichloromethane (50ml). The combined organic components were dried over magnesium sulphate and concentrated under reduced pressure to give the title compound as a cream solid (4.2g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.92 (m, 2H), 1.19 (m, 2H), 1.78 (m, 1H), 1.99 (s, 3H), 7.47 (m, 2H), 7.62 (m, 1H).
LRMS (electrospray) : m/z [M-H$^+$] 267.

PREPARATION 8

5-[(3-Cyclopropyl-5-methyl-1*H*-pyrazol-4-yl)oxy]isophthalonitrile

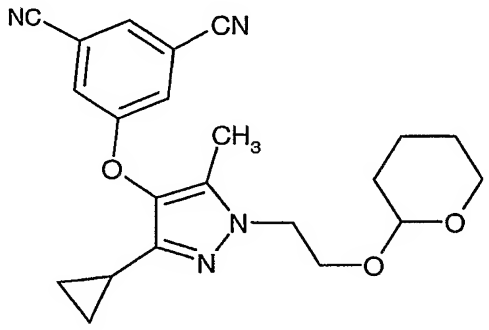


Hydrazine hydrate (298µl, 6.16mmol) was added to a solution of the diketone from Preparation 7 (1.50g, 5.60mmol) in acetic acid (22ml) under nitrogen at room temperature. After stirring at 50 °C for 18 hours, the mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was partitioned between 10% aqueous potassium carbonate solution (50ml) and dichloromethane (50ml). The separated aqueous layer was washed twice with dichloromethane (2x50ml). The combined organic components were dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide a pale yellow oil. The crude product mixture was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (75:25 changing to 67:33, by volume) to provide the title compound (1.20g) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.75 (m, 2H), 0.85 (m, 2H), 1.60 (m, 1H), 2.10 (s, 3H), 7.40 (s, 2H), 7.60 (s, 1H).
LRMS (thermospray): m/z [MH$^+$] 260.

PREPARATION 9

5-({3-Cyclopropyl-5-methyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)isophthalonitrile



To a stirred solution of the pyrazole from Preparation 8 (420mg, 1.59mmol) in dimethylformamide (4ml) at 0°C was added sodium hydride (70mg of a 60% w/w suspension in mineral oil). After the addition was complete the cooling bath was removed and the mixture was stirred at room temperature for 30 minutes. A solution of 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (264µl, 1.75mmol) in dimethylformamide (2ml) was added. After 2 hours the reaction mixture was quenched by addition of water (20ml) and was extracted with dichloromethane (3 x 20ml). The combined organic components were washed with brine (2 x 20ml), dried over magnesium sulfate, filtered and concentrated to give a yellow oil. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0 changing to 98:2, by volume) to provide a mixture of the two regioisomers (594mg). The two regioisomers were separated by flash chromatography on silica gel eluting with toluene:ethyl acetate (100:0 changing to 80:20, 75:25, 67:33 and 50:50 by volume) to provide the title compound (257mg) (less polar fraction) and its regioisomer (90mg) (more polar fraction).

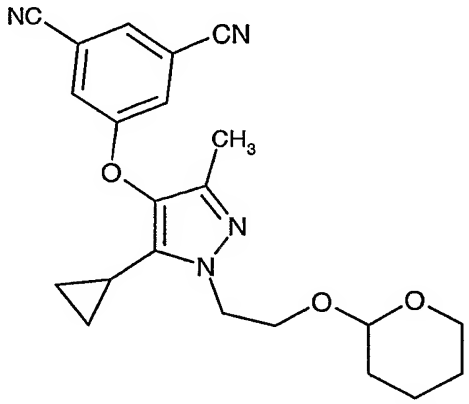
Less Polar Fraction

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.78 (m, 4H), 1.55 (m, 5H), 1.67 (m, 2H), 2.12 (s, 3H), 3.45 (m, 1H), 3.65 (m, 1H), 3.75 (m, 1H), 4.04 (m, 1H), 4.18 (m, 2H), 4.53 (m, 1H), 7.40 (s, 2H), 7.59 (s, 1H).

LRMS (thermospray): m/z [MH^+] 393.

More Polar Fraction

5-({5-Cyclopropyl-3-methyl-1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-pyrazol-4-yl}oxy)isophthalonitrile

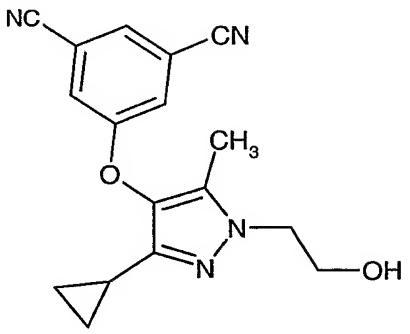


^{1}H NMR (300MHz, $CDCl_3$): δ = 0.68 (m, 2H), 0.85 (m, 2H), 1.53 (m, 3H), 1.72 (m, 4H), 2.10 (s, 3H), 3.51 (m, 1H), 3.72 (m, 1H), 3.83 (m, 1H), 4.17 (m, 1H), 4.35 (m, 2H), 4.58 (m, 1H), 7.38 (s, 2H), 7.59 (s, 1H).

LRMS (thermospray): m/z [MH^+] 393.

CLAIMS

1. The compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof.

2. A pharmaceutical composition including the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

3. A pharmaceutical composition according to claim 2 including one or more additional therapeutic agents.

4. The compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for use as a medicament.

5. The compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for use as a reverse transcriptase inhibitor or modulator.

6. The compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for use in the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS).

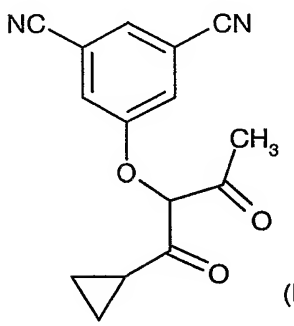
7. Use of the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity.

8. Use of the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for the manufacture of a medicament for the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS).

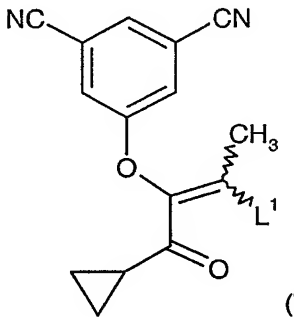
9. A method of treating an HIV or a genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS), comprising administering an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3.

10. A process for preparing the compound of formula (I) or a salt, solvate or pharmaceutically acceptable derivative thereof, which comprises:

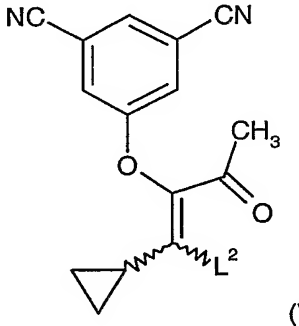
(A) condensation of a compound of formulae (II), (VI) or (VII)



(II)



(VI)



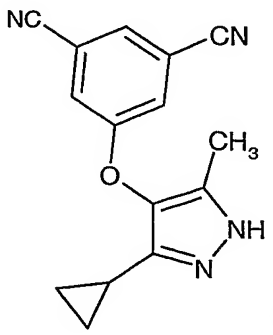
(VII)

with the compound of formula (V)

$$H_2NNHCH_2CH_2OH \quad (V)$$

or a salt or hydrate thereof;

(B) alkylation of the pyrazole of formula (XIII)



(XIII)

with an alkylating agent of formula (XIV)

$$Lg\text{-}CH_2CH_2OH \quad (XIV)$$

or a protected derivative thereof;

(C) deprotecting a protected derivative of the compound of formula (I);

and optionally converting the compound of formula (I) prepared by any one of processes (A) to (C) into pharmaceutically acceptable salt, solvate or derivative thereof.

11. A compound of formulae (II), (VI), (VII), (VIII), (IX) or (XIII).

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IB 03/03946

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 A61P31/18 C07D231/18 C07C255/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 085860 A (PRICE DAVIS ANTHONY ;PFIZER LTD (GB); JONES LYN HOWARD (GB); MOWBR) 31 October 2002 (2002-10-31) cited in the application page 13, formulae (VIII) and (IX) claims 1,37; examples 96,168 ---	1-11
A	WO 02 04424 A (CORBAU ROMUALD GASTON ;PFIZER LTD (GB); WOOD ANTHONY (GB); MOWBRAY) 17 January 2002 (2002-01-17) claim 1 ---	1-11
A	US 3 303 200 A (FLANIGAN DONALD J ET AL) 7 February 1967 (1967-02-07) cited in the application column 2, line 4; claim 1 -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2003	26/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Johnson, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/03946

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,2,4-11 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,4-11 (all part)

Claims 1,2 and 4-10 contain the term "pharmaceutically acceptable derivative" of formula (I). The scope of the claims is not clear, as this term does not have a generally acceptable meaning in the field. Various derivative groups are given on p. 2 which are apparently modifications of the functional groups in the compound of formula (I). However, the only functional group which appears susceptible to the disclosed modification is the hydroxy group. For this reason the search has been performed for the compounds of formula (I) and their derivatives in which the hydrogen atom of hydroxy group is replaced by another group.

The compounds of formulae (VI) and (VII) contain the variable groups L1 and L2, which are defined on pp. 4-5 of the application as being "suitable leaving groups". Claim 11 is a product claim which gives absolute protection for the compounds defined therein. The term "suitable leaving group" can only be understood in the context of a process claim, in which the conditions under which the group should leave are defined. Thus the term "suitable leaving group" in claim 11 is unclear, as the compounds of formulae (VI) and (VII) are not defined in terms of process parameters. Compounds (VI) and (VII) have therefore been searched only insofar as the groups L1 and L2 are clearly defined, namely wherein these groups are di(C1-C6)alkylamino groups, as defined on p. 5, l. 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati	Application No
PCT/IB	03/03946

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02085860 A	31-10-2002	WO 02085860 A1	31-10-2002
		US 2003100554 A1	29-05-2003
WO 0204424 A	17-01-2002	AU 6776601 A	21-01-2002
		BR 0112252 A	02-09-2003
		CA 2415492 A1	17-01-2002
		EP 1299361 A1	09-04-2003
		WO 0204424 A1	17-01-2002
		US 2002032184 A1	14-03-2002
US 3303200 A	07-02-1967	NONE	